Multivalent ligands control stem cell behaviour in vitro and in vivo.

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Public Summary:
There is broad interest in designing nanostructured materials that can interact with cells and regulate key downstream functions, especially for controlling stem cells for therapeutic application. In particular, materials with nanoscale features may enable control over multivalent interactions, which involve the simultaneous binding of multiple ligands on one entity to multiple receptors on another and are ubiquitous throughout biology. Cellular signal transduction of growth factor and morphogen cues (which have critical roles in regulating cell function and fate) often begins with such multivalent binding of ligands, either secreted or cell-surface-tethered to target cell receptors, leading to receptor clustering. Cellular mechanisms that orchestrate ligand-receptor oligomerization are complex, however, so the capacity to control multivalent interactions and thereby modulate key signalling events within living systems is currently very limited. Here, we demonstrate the design of potent multivalent conjugates that can organize stem cell receptors into nanoscale clusters and control stem cell behaviour in culture and in the brain. The receptor-binding domain of ephrin-B2 was conjugated to a soluble biopolymer to yield multivalent nanoscale conjugates that potently induce signalling in neural stem cells and promote their neuronal differentiation both in culture and within the brain. We also found that synthetic multivalent conjugates of ephrin-B1 strongly enhance human embryonic and induced pluripotent stem cell differentiation into functional dopaminergic neurons. Multivalent bioconjugates are therefore powerful tools and potential nanoscale therapeutics for controlling the behaviour of target stem cells in vitro and in vivo.

Scientific Abstract:
There is broad interest in designing nanostructured materials that can interact with cells and regulate key downstream functions. In particular, materials with nanoscale features may enable control over multivalent interactions, which involve the simultaneous binding of multiple ligands on one entity to multiple receptors on another and are ubiquitous throughout biology. Cellular signal transduction of growth factor and morphogen cues (which have critical roles in regulating cell function and fate) often begins with such multivalent binding of ligands, either secreted or cell-surface-tethered to target cell receptors, leading to receptor clustering. Cellular mechanisms that orchestrate ligand-receptor oligomerization are complex, however, so the capacity to control multivalent interactions and thereby modulate key signalling events within living systems is currently very limited. Here, we demonstrate the design of potent multivalent conjugates that can organize stem cell receptors into nanoscale clusters and control stem cell behaviour in vitro and in vivo. The ectodomain of ephrin-B2, normally an integral membrane protein ligand, was conjugated to a soluble biopolymer to yield multivalent nanoscale conjugates that potently induce signalling in neural stem cells and promote their neuronal differentiation both in culture and within the brain. Super-resolution microscopy analysis yielded insights into the organization of the receptor-ligand clusters at the nanoscale. We also found that synthetic multivalent conjugates of ephrin-B1 strongly enhance human embryonic and induced pluripotent stem cell differentiation into functional dopaminergic neurons. Multivalent bioconjugates are therefore powerful tools and potential nanoscale therapeutics for controlling the behaviour of target stem cells in vitro and in vivo.